White matter integrity assessed by diffusion tensor tractography in a patient with a large tumour mass but minimal clinical and neuropsychological deficits

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Summary

Diffusion tensor imaging (DTI) tractography and image registration were used to investigate a patient with a massive left-sided brain tumor, whose size was largely disproportionate to his subtle neurological deficits. MRI was obtained from the patient and his healthy identical twin, who acted as anatomical reference for DTI and as a control for quantitative measures. To compensate for the patient's altered anatomy, seed and way points for probabilistic tractography were drawn on the color-coded direction maps of the healthy twin. Registration, based on the combination of b_0-images, T2-weighted and T1-weighted images, was used to identify the corresponding regions in the patient. The corticospinal tract (CST), the superior longitudinal fasciculus (SLF), and the cingulum bundle (CB) showed displaced anatomy. A significant difference was found between fractional anisotropy distribution along the left SLF and CB, but not along the CST. These findings fit well with the patient's substantial preservation of his motor abilities, while abnormalities of the SLF and CB could explain the subtle but detectable cognitive deficits.

KEY WORDS: brain lesion, cognition, DTI, image registration, tractography

Introduction

Brain lesions may result in either very profound or subtle neurological deficits, depending on their size, location, growth rate and character (Alomar, 2010). The growth rate of low-grade tumors is known to be one of the most important factors determining subsequent malignant transformation, which eventually causes clinical deficits (Rees et al., 2009). This can be explained by the extraordinary plasticity of brain tissue, which can compensate for slowly occurring anatomical changes. Diffusion tensor imaging (DTI) is a novel magnetic resonance imaging (MRI) technique that allows the measurement of water self-diffusivity (and thus of the interactions between water molecules and obstacles that hinder their motion) and gives information about the size, orientation and shape of brain structures *in vivo* (Basser et al., 1994). Several useful indices can be derived from DTI, including fractional anisotropy (FA), which measures intra-voxel directional coherence. FA is often used as a measure of tissue integrity and organization (Pierpaoli and Basser, 1996). The ability of DTI to reflect the underlying tissue structure also leads to the possibility of tracing fiber tracts in white matter (WM), based on the assumption that the principal direction of diffusion is parallel to the main fiber direction (DTI tractography) (Conturo et al., 1999). DTI tractography is therefore a unique tool for *in vivo* WM tract reconstruction, which can measure structural integrity along specific anatomical pathways. In this study, we used DTI in conjunction with image registration to investigate the paradoxical case of a patient suffering from a diffuse WHO grade II astrocytoma, whose size and location were largely disproportionate to the subtle neurological and cognitive deficits presented. The individual reported in this case study is a monozygotic (MZ) twin, providing a unique opportunity to compare two individuals (with and without tumor) raised in the same environment and having an identical genetic complement. Studies have shown that MZ twins have very similar overall brain size and shape, although the sulci and gyri of MZ brains are likely to be influenced by non-genetic effects as well (Mohr et al., 2004). The gray matter (GM) and WM volumes in all four lobes, the cerebellum and subcortical structures are also reported to be highly correlated in healthy MZ twins (Carmelli et al., 1998; White et al., 2002). A review of longitudinal studies in twins, exploring the relative impact of genetic and non-genetic factors on brain anatomy, concludes that heritability is high, and shared environmental effects are low for most brain morphometric measures (Giedd et al., 2007). Although it is possible that a broad range of environmental exposures may also affect neuroanatomical phenotypes, as explained below, the subjects included in

this study were, as mentioned, raised in the same environment. Therefore, using image registration to correct for anatomical distortion between the twins, the healthy identical twin was able to act both as an anatomical reference for DTI and as a control for quantitative measures in the patient. Tract-specific measures of FA distribution were obtained from the twins, and quantitative comparisons of FA distribution from three major WM tracts were performed, showing a relative preservation of WM integrity in the patient, particularly along the motor pathways.

Materials and methods

Case study

YG is a 32-year-old, right handed male who works as an office clerk. Four years before the current study, he was admitted to the Accident and Emergency Department after a series of adversive seizures during which he was fully conscious but reported feeling 'out of control'. On admission, YG had slightly slurred speech, word finding difficulties, and some expressive dysphasia. However, this had disappeared by the time he took part in this study. On neurological examination, he presented only an increase of the reflexes in the right limbs, in the absence of abnormalities in muscle tone and power. He did not show any limitation in his motor ability, and his gait was completely normal. A clinical MRI scan revealed the presence of a large mass in the left lateral (middle frontal gyrus) and left medial (superior frontal gyrus, subgenu and cingulate cortex) frontal lobe. The mass had caused both a shift to the right of the midline and compression of the body of the corpus callosum. As the inner table of the skull appeared scalloped, it was deemed likely that the tumor had been present for many years. A left minicraniotomy and stealth-guided biopsy confirmed the diagnosis of a diffuse WHO grade II astrocytoma. Due to the tumor size, a conservative approach to YG's treatment was adopted, where attempts were made to control his seizures rather than resect the tumor. YG was reviewed for four years (at six-month intervals) by a neuro-oncologist, before taking part in the current study. Each visit was accompanied by conventional MRI scanning. His clinical and neurological status has remained substantially unchanged. Conversely, serial MRI scans revealed a growth rate acceleration from 7-12% in the first two years, to 34-37% in the last two years, but without the development of any neurological deficits or detectable changes on neurological examination.

Four years after his first admission to the Accident and Emergency Department, YG and his identical twin brother took part in this study. Written consent was obtained according to the Declaration of Helsinki and the study was approved by the National Hospital for Neurology and Neurosurgery & Institute of Neurology Joint Research Ethics Committee. Both brothers underwent an extensive neuropsychological assessment and an MRI examination at 3T. As they were raised together and had similar socioeconomic and educational backgrounds, using YG's twin brother controlled for environmental effects.

Neuropsychological investigation

YG's performance on the neuropsychological battery is detailed in table 1. Descriptions of tests, procedures and norms can be found in the individual sources cited. His premorbid level of functioning was estimated as being in the average range using the National Adult Reading Test (Nelson and Willison, 1991). His nonverbal abstract reasoning was assessed using the Raven's Advanced Progressive Matrices (Raven et al., 1998), and he obtained a high average score. His performance on both the Graded Naming Test (GNT) (McKenna and Warrington, 1980) and the Graded Difficulty Arithmetic test (Jackson and Warrington, 1986) was normal. His visual perceptual abilities were intact with an adequate score on the Fragmented Letters subtest of the Visual Object and Space Perception Battery (Warrington and James, 1991). Verbal and visual recall and recognition memory functions were evaluated and compared using the Doors and People test (Baddeley et al., 1994). Verbal and visual recognition memory were assessed using the Names subtest and the Doors subtest, respectively. Verbal and visual recall memory were assessed using the People subtest and the Shapes subtest, respectively. His verbal recall performance was impaired, yet he performed within normal limits on the visual recall and verbal and visual recognition memory subtests. As regards executive abilities, YG demonstrated a reduction in verbal fluency using Controlled Oral Word Association (letters F, A and S) (Spreen and Strauss, 1998), producing 25 words in total for letters F, A and S ($<10^{th}$ percentile). Yet, he performed within normal limits on the remaining frontal executive tasks. For example, his Stroop Color-Word Test score (Trenarry et al., 1998) and his Trail Making Test (Reitan and Wolfson, 2004) performance were normal. His speed of processing was normal on Part A of the Trail Making Test. He performed within the high average range on the Brixton Spatial Anticipation Test and within the moderate average range on the Hayling Sentence Completion Test (Burgess and Shallice, 1996). YG's identical healthy twin brother underwent the same neuropsychological assessment, performing within normal limits on all tests (Table 1).

MRI acquisition and analysis

MRI was performed at 3T using a Siemens Magnetom Allegra (Siemens Medical Solutions, Erlangen, Germany) equipped with a circularly polarized transmit-receive coil. The maximum gradient strength was 40 mT m^{-1}, with a maximum slew rate of 400 mT m^{-1} μs^{-1}. Both YG and his twin brother underwent the same MRI acquisition protocol to obtain: a T2-weighted scan (T2W), a 3D T1-weighted (T1W) volume, and a DTI sequence (single-shot EPI, no. of diffusion directions=61, with 7 b_0 images, max b factor = 1000 smm^{-2}; TE=85 ms, isotropic resolution=2.3mm^3).

DTI data were processed using the Camino package (Cook et al., 2006) and the probabilistic tractography algorithm PICo (Parker et al., 2003). For every voxel in the brain, PICo assigns a probability of being connected to the voxels included in a region of interest (ROI) selected a priori, named the "seed point" ROI. The reconstructed fiber tract can be further constrained by defining "way

point" ROIs. Pathways which do not reach or cross the way point ROIs are discarded. The definition of seed point and way point ROIs is the only operator-dependent step, and can be particularly challenging in the presence of masses that alter the anatomy. To compensate for this problem in this study, seed and way point ROIs were manually drawn on the color-coded direction maps of the healthy twin. A registration approach was then used to find the corresponding regions in the patient. The registration utilized the high-resolution structural scans to accurately map distorted anatomy between subjects: CONTROL:{DTI(b_0) $\rightarrow$ T2W $\rightarrow$ T1W} $\rightarrow$ {T1W $\rightarrow$ T2W $\rightarrow$ DTI(b_0)}:PATIENT. Within-subject registrations used FLIRT (Jenkinson et al., 2002). Between-subject registrations used FLIRT followed by an optimized non-rigid fluid-based approach, which can compensate for highly deformed anatomy (Freeborough and Fox, 1998; Crum et al., 2005).

The FLIRT registrations corrected for global differences between scans arising from different fields of view, voxel dimensions and patient positioning. The non-rigid registration determined a coordinate transformation which matched corresponding brain structures from YG to his healthy twin allowing consistent seed points to be defined; it explicitly compensated for the mechanical effect of the mass. Seed points were mapped back into the original diffusion images for tractography. PICo was used to reconstruct three main fiber bundles, bilaterally, in both subjects (by means of connectivity maps): i) the corticospinal tract (CST), ii) the superior longitudinal fasciculus (SLF), and iii) the cingulum bundle (CB). The following criteria were used to select seed and way points (Wakana et al., 2007). For the CST, seeds were manually drawn in the cerebral peduncles, and way points encompassed the sensory-motor cortex. For the SLF, seeds were placed dorsolateral to the putamen, on a coronal slice corresponding to the central part of the body of the corpus callosum, to encompass voxels where fibers had a mainly anterior-posterior direction as shown by color coding, while way points included fibers with an anterior-posterior direction at the level of the splenium of the corpus callosum. For the CB, seeds were placed rostral to the genu of the corpus callosum, and way points were placed rostral to the splenium, including all voxels with a mainly anterior-posterior direction. Figure 1 (over) shows the location of the seed and way points for the three tracts (only for the left hemisphere). A tract-specific mask indentifying all the voxels belonging to each WM bundle was obtained by retaining voxels having a higher than 0.2 probability of connection to the seed point ROI. FA distribution along each tract was characterized and compared between the twins in two ways: first by computing its various moments (mean, standard deviation, skewness and kurtosis), and second by comparing the set of FA values obtained from all the voxels in each tract, using a Kolmogorov-Smirnov test (Press et al.,1992). This is a non-parametric method of comparing two samples, which is sensitive to differences in both location and shape of the empirical cumulative distribution functions of the two samples. This procedure was carried out to compare the FA distraction of the three tracts in the patient's left hemisphere (lesion side) with i) the tracts in the contralateral hemisphere and ii) the tracts in the left hemisphere of the healthy twin. A p-value lower than 0.01 was considered significant.

Results

Conventional MRI images showed the macroscopic features of the tumor mass (Fig. 2, over). On T2W images,

Table 1 - Performance of patient YG and his healthy twin brother on the neuropsychological battery.

	Patient YG	Healthy Twin
NART Premorbid IQ	100	100
Raven's Advanced Progressive Matrices (max = 12)	10	10
Graded Naming Test (max = 30)	19	19
Graded Difficulty Arithmetic test (max = 24)	14	16
Fragmented Letters (max = 20)	18	20
Doors & People		
People scaled score (verbal recall)	4[a]	11
Names scaled score (verbal recognition)	12	12
Shapes scaled score (visual recall)	10	7
Doors scaled score (visual recognition)	11	9
Verbal Fluency	25[b]	41
Stroop Color-Word Test score (max = 112)	102	112
Trail Making Test A (s)	33	33
Trail Making Test B (s)	54	47
Brixton Spatial Anticipation Test scaled score	7	6
Hayling Sentence Completion Test scaled score	5	4

Abbreviations and symbols: NART=National Adult Reading Test; (s)=seconds; [a] <5th percentile; [b] <10th percentile.

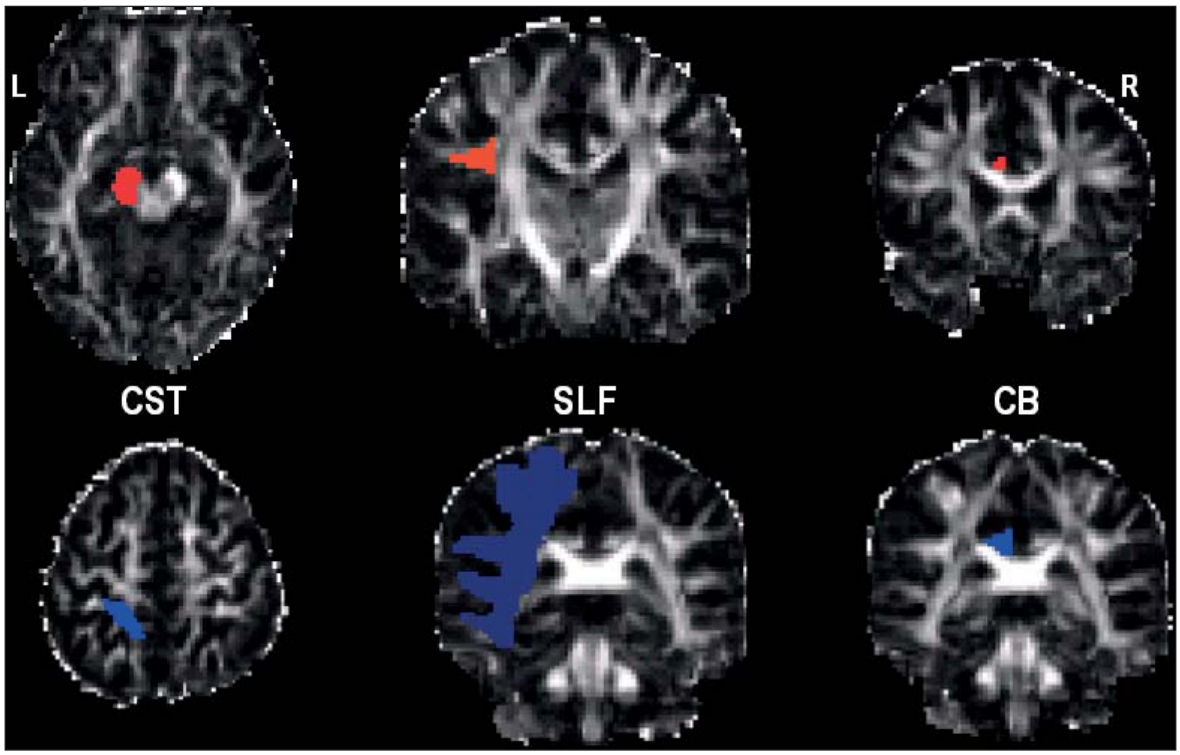

Figure 1 - Seed (red) and way (blue) points used for tractography. The regions were selected following the guidelines in Wakana et al. (2007). CST=corticospinal tract; SLF=superior longitudinal fasciculus; CB=cingulum bundle; L=left; R=right.

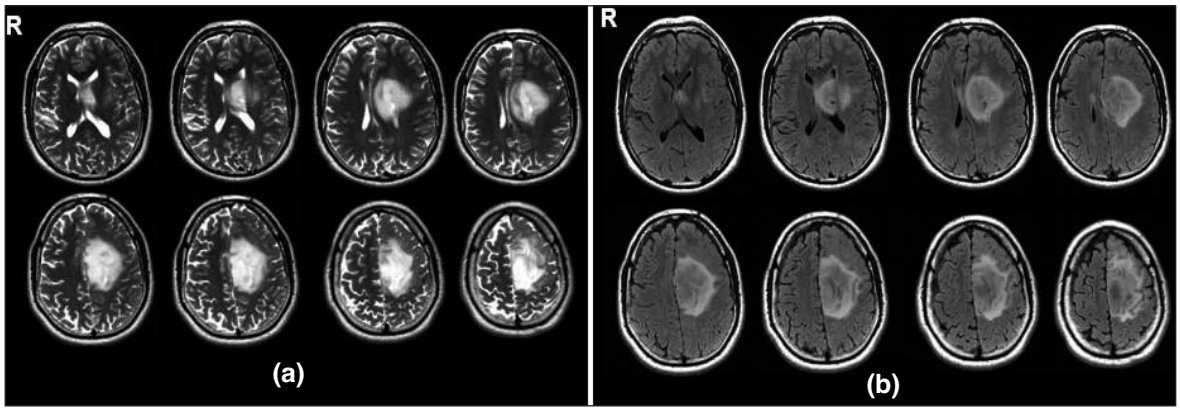

Figure 2 - Anatomical localization of the brain lesion as assessed by T2-weighted (panel a) and fluid attenuated inversion recovery scans (panel b). The large mass is located in the left lateral (middle frontal gyrus) and medial frontal lobe (superior frontal gyrus, subgenu and cingulate cortex), and causes a shift to the right of the midline and compression of the body of the corpus callosum. See text for further details.

cross-section diameters of the tumor lesion were: 7.1 and 6.4, cm in the anteroposterior and laterolateal projections respectively. Despite its large size, the tumor mass did not appear to infiltrate any true eloquent structure of the brain. The between-subjects registration successfully matched normal brain tissue (Fig. 3). Despite the lesion, the three tracts were successfully reconstructed in the left hemisphere, showing a displaced anatomy consistent with the presence of the tumor (Fig. 4, over).

As further confirmation of the correct reconstruction of the left CST in the patient, figure 5 (over) shows the probabilistic map of the tract overlaid onto a co-registered T1W image, demonstrating that the tract correctly projects to the precentral sulcus.

Table 2 shows the statistics summarizing the distribution of FA along each considered tract in both twins. When comparing the FA distribution between left and right hemisphere tracts of the patient, the Kolmogorov-Smirnov test showed no significant between-side difference in the distribution of FA in the CST (p=0.1), while the diffe-

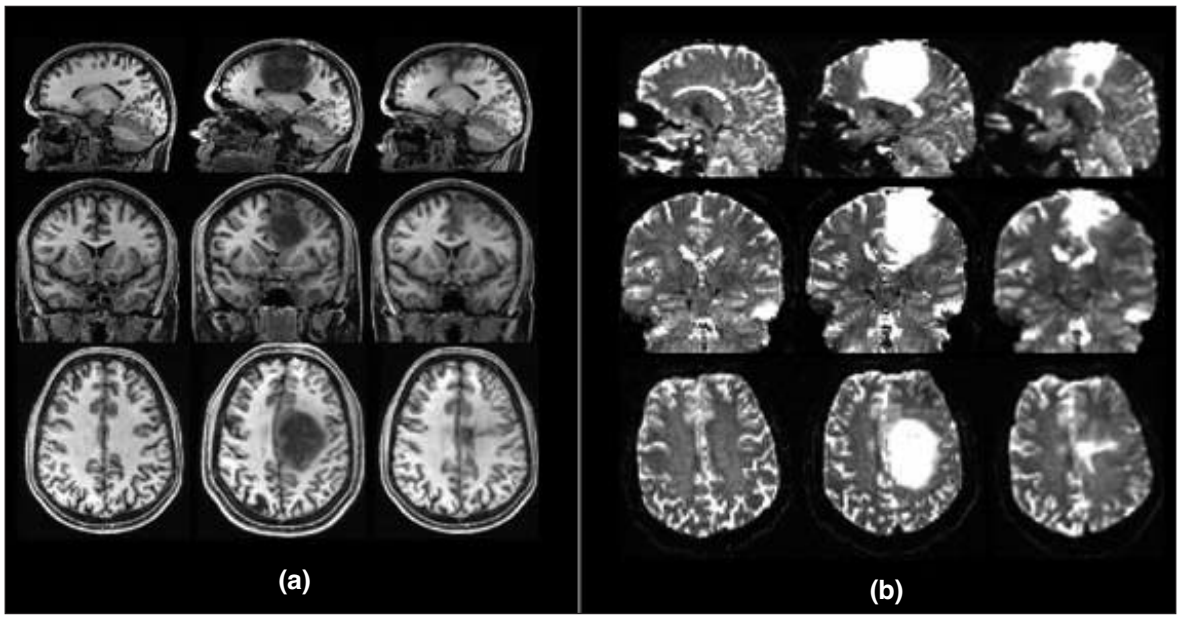

Figure 3 - Non-rigid registration removes neuroanatomical distortion caused by the tumor by matching normal structures in YG to those in the healthy twin: (a) T1-weighted images (b) b_0 images. In both panels, left=healthy twin, middle=affected twin, right=affected twin after registration to the healthy twin. Registered images allowed anatomically consistent seed points to be defined which were mapped back onto the original diffusion images for tractography. See text for further details.

Table 2 - First four moments of FA distribution along each of the reconstructed tracts, for the patient and his identical twin.

		CST		SLF		CB	
		Left	Right	Left	Right	Left	Right
Patient	Mean FA	0.48	0.50	0.38	0.42	0.32	0.45
	FA SD	0.19	0.20	0.18	0.19	0.17	0.23
	FA skewness	-0.078	-0.083	0.156	-0.184	0.732	0.015
	FA kurtosis	2.17	2.14	2.35	2.32	2.78	1.82
	No. Voxels	817	688	1697	1309	721	222
Healthy twin	Mean FA	0.46	0.46	0.36	0.38	0.32	0.37
	FA SD	0.19	0.20	0.17	0.17	0.20	0.20
	FA skewness	-0.045	-0.109	0.018	0.107	0.469	0.221
	FA kurtosis	2.38	2.35	2.16	2.36	2.00	2.09
	No. Voxels	1539	1382	1683	1427	276	333

Abbreviations: FA=fractional anisotropy; SD=standard deviation, CST=corticospinal tract; SLF=superior longitudinal fasciculus; CB=cingulum bundle.
Skewness is a measure of the asymmetry of the distribution, with zero indicating perfect symmetry, and negative values indicating that more observations lie to the right than to the left of the mean. Kurtosis is a measure of the sharpness of the peak of the distribution, with higher values indicating a sharper peak.

rence was significant for both the SLF (p=0.001) and the CB (p<0.001). When comparing FA distribution between the tracts of the patient and the healthy twin, the Kolmogorov-Smirnov test showed no significant between-subject difference in the distribution of FA in the left CST (p=0.08), suggesting a relative preservation of WM integrity along the tract, despite the displacement caused by the tumor. By contrast, a significant difference was found between FA distribution along the SLF (p=0.002) and the CB (p=0.0009).

Discussion

The DTI technique allows direct insight into the subtle anomalies in WM connectivity which may be induced by lesions such as brain tumors. The connectivity concept rests on the evidence that WM lesions may result in brain dysfunction even in the presence of intact GM areas (disconnection syndrome). With respect to cognition, this concept has become clearer with the demonstration of functional networks believed to subserve higher level functions (Greicius et al., 2003). Although the relationship between structural and functional disconnection is still a matter of debate, it has recently been suggested that some GM regions may become atrophic due to structural brain disconnection (Gili et al., 2011). In this study, the distinct effects of a grade II astrocytoma involving the medial and lateral subdivisions of the frontal lobe were investigated on the CST, SLF and CB WM tracts using DTI. DTI is an established technique for investigating WM integrity, but its application in abnormal anatomy is challenging. In the case of patient YG, we were able to use his identical twin brother as a closely matched control in order to obtain, with high confidence, anatomical ROIs in a highly abnormal patient. Within the potential limitations of DTI (i.e., the relative insensitivity of tractography to accurately track WM pathways within a neoplasm), the results of the tractography suggest that despite the large mechanical displacement of the tracts, the main pathways supported by these three WM bundles are relatively preserved. In particular, the CST was found to retain its structural integrity, as shown by preserved FA distribution along the tract. The FA distribution along the SLF and the CB, on the other hand, differed between the twins. Evaluation of the various moments of the distribution (Table 2) suggested that the differences are subtle and likely to be confined to the tails of the distribution. Consistently, previous assessment of DTI-derived measures (including FA) in WM regions near glioblastomas encompassing the CST has shown that these measures correlate with the presence of symptoms (Romano et al., 2008).

The neuropsychological investigation of the patient (YG) revealed a preserved performance on the majority of the neuropsychological measures he was assessed on, including IQ, language, memory and executive abilities. However, he performed poorly on a test of verbal recall. Free recall requires participants to initiate effective retrieval strategies, to organize thinking and weigh up the search results. Impairments of this kind, often reported in patients with frontal lobe lesions, are thought to be secondary to impairments in frontal-based supervisory processes, rather than being pure memory deficits (Dimitrov et al., 1999; Janowsky et al., 1989; Jetter et al., 1986; Shimamura et al., 1990; Wheeler et al., 1995). Patient YG's lesion involves the left lateral middle frontal gyrus, superior medial frontal gyrus, subgenu and cingulate cortex, and from this perspective it is interesting to note that studies examining the anatomical specificity of free recall in frontal patients have shown that deficits in strategic memory retrieval are associated with lesions in the medial and lateral prefrontal cortex (Alexander et al., 2003; Turner et al., 2007; MacPherson et al., 2008).

Patient YG also performed poorly in terms of verbal fluency, which is often used to assess frontal executive

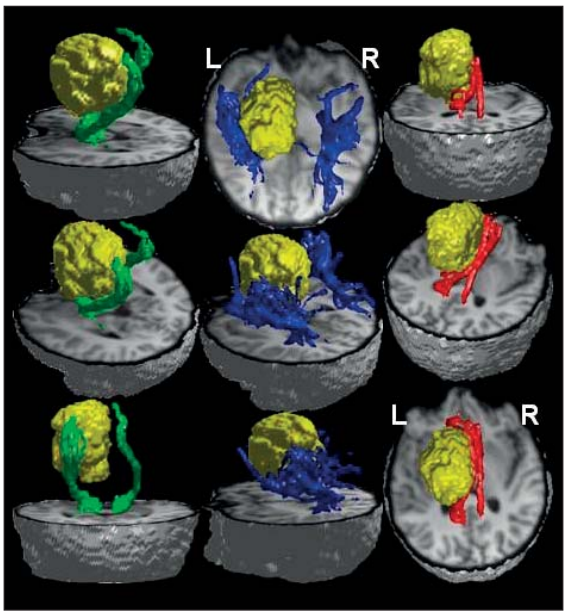

Figure 4 - Results of tractography in the patient's brain. The figure shows the three-dimensional isosurface plot of voxels with a greater than 20% probability of connection to the seed points. The corticospinal tracts (left column, in green), the superior longitudinal fasciculi (central column, in blue), and the cingulum bundles (left column, in red) are shown together with a three-dimensional reconstruction of the tumor (in yellow). See text for further details.

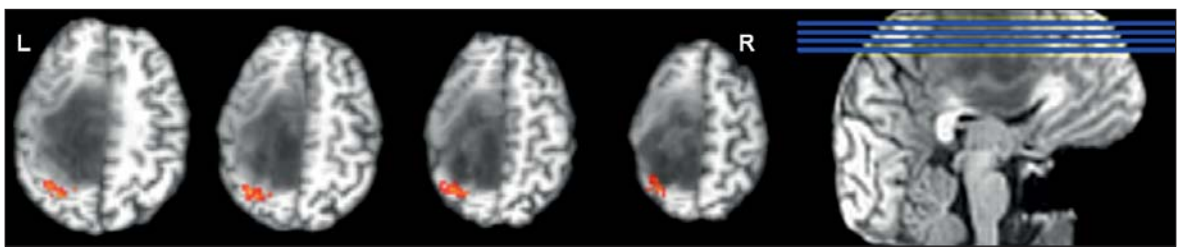

Figure 5 - Probabilistic reconstruction of the corticospinal tract (CST) in the left hemisphere of the patient. Despite distorted anatomy due to the presence of the lesion, the CST correctly projects to the precentral sulcus, confirming the successful reconstruction of the whole tract.

abilities. Previous neuroimaging studies have demonstrated activation in the left dorsolateral prefrontal cortex (Frith et al., 1991; Frith et al., 1995; Warkentin and Passant, 1997), the anterior cingulate (Frith et al., 1991; Frith et al., 1995; Phelps et al., 1997), and left inferior frontal gyrus during verbal fluency performance (Phelps et al., 1997). YG's poor performance on verbal fluency could also be linked to his deficit in initiating retrieval strategies (Estes, 1974; Laine, 1998; Troyer et al., 1997), which are also known to be controlled by frontal executive functions. However, it is unlikely that his impairment is due to a deficit in word retrieval as he performed well on other tasks thought to rely on word retrieval, such as the Hayling Sentence Completion test and the GNT.

Moving on to potential cognitive deficits that might arise from damage to the distributed networks, the results of the tractography suggest that the CST, SLF and CB WM bundles are relatively preserved, although there may be a small reduction in WM integrity in the SLF and CB. The SLF connects the middle frontal gyrus/dorsolateral prefrontal cortex (Brodmann areas 9 and 46), which supports expressive language, with areas of the parietal and temporal cortex that support receptive language function. Patients with damage to this pathway typically report impairment of phonologically based language functions such as the ability to repeat spoken language (Breier et al., 2008). Although we did not formally assess YG, he did not appear to have any word repetition difficulties. The CB connects the cingulate cortex with various brain regions such as the frontal, parietal and temporal structures and it is the most prominent WM fiber tract in the limbic system (Mufson and Pandya, 1984). The left CB is thought to carry connections important for frontal executive processes, as studies have found significant correlations between performance on frontal executive tests such as the Trail Making Test and Digit Symbol Test and mean diffusivity in the left cingulum (O'Sullivan et al., 2005). The fact that YG showed no decline on the majority of frontal executive measures, despite the presence of a large left frontal mass, was somewhat surprising. It may be that the subtle effects on the WM integrity of the CB were not sufficient to disrupt YG's frontal executive abilities. Recently, researchers have argued that the maximum lesion site overlap in group studies may extend into WM pathways that interconnect with other brain regions. Therefore, it is likely that the critical factor in neuropsychological studies is not necessarily the overlap in the cortical region that is damaged but the disconnection between different brain areas. Clearly, it is important to investigate both cortical and WM pathway damage if we are to truly understand the neuroanatomy of cognition.

Another reason for YG's intact frontal executive abilities may be that his tumor involves only the middle frontal gyrus, and not the inferior frontal gyrus. The middle and inferior frontal gyri together make up the dorsolateral prefrontal cortex, which is thought to play an important role in frontal executive abilities (Petrides and Pandya, 2002). The fact that YG's entire right dorsolateral prefrontal cortex and left inferior frontal gyrus are both spared might explain his normal performance on the majority of frontal executive measures.

This study was possible thanks to the special circumstance of YG having an identical twin. On the one hand, this clearly limits the possibility of generalizing the same approach to other patients. On the other, this is a proof of concept study, exploring the possibility of investigating by quantitative DTI tractography the impact of tumor lesions on surrounding WM tracts. This study is therefore expected to prompt future research with the aim of creating imaging templates, specific for patient age and gender, to be used as a reference to assess the lesion effect on a single subject basis. This might eventually have an impact on patients' surgical planning.

Finally, it is important to reiterate that our results must be interpreted within the well-known limitations of DTI tractography. In general, the tensor model is a simplification of reality, unable to resolve multiple WM fiber directions within the same voxel. For this reason, tractography algorithms perform poorly in regions of fiber crossing or complexity or in regions with small or tortuous pathways. Additional problems can be encountered when dealing with a large neoplastic mass like the one described in this study. The tumor certainly caused a reduction in diffusion anisotropy and, as a consequence, part of the tracts adjacent to the mass might have been artificially interrupted; similarly, we cannot rule out the possibility that part of the tracts we tried to reconstruct was missed. Nevertheless, the use of a probabilistic tractography algorithm should increase the chances of capturing most of the trajectories belonging to the tract. Furthermore, the consistency between the reconstructed tracts and known anatomy (e.g., Fig. 5) suggests that our results are convincing.

In conclusion, DTI is an established technique for investigating WM integrity but its application in abnormal anatomy remains challenging. In this case of a patient with a large brain lesion but minimal neurological deficits, tractography played an important role in confirming that, despite the large mechanical displacement of the tracts, eloquent structures had not been invaded by the mass. In particular, the corticospinal tract retained its structural integrity, as shown by preserved FA distribution along the tract. This result is consistent with the neurological examination. The FA distribution along the SLF and the CB, on the other hand, differed between the twins. Evaluation of the various moments of the distribution (Table 1) suggested that the differences are subtle and likely to be confined to the tails of the distribution. These subtle differences in FA of the SLF and CB fit well with the cognitive profile of the patient.

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